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Realities and Virtual Realities of Inborn Errors of Metabolism: Biochemical Genetics in the Molecular Genetic Era

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INTRODUCTION

Genetics is concerned with the storage, transmission, and translation of the heritable information which determines development, function, and variation of living organisms. Medical genetics, as a special area of human genetics, is concerned with genes which in their normal form confer health, and in their variant forms can bring about disease. Not long after Mendel's work was rediscovered, William Bateson prophesied that an understanding of the laws of heredity would bring about more change in man's outlook on the world, and in his power over nature, than any other foreseeable advance in knowledge about nature. At the same time, Archibald Garrod introduced his concepts about inborn errors of metabolism, chemical individuality, and "diathesis" (susceptibility to disease). By examples drawn from his patients, Garrod illustrated Bateson's precept. In his own way, David Danks has been both a Bateson and a Garrod to Australian medical genetics.

I

A search of the OMIM database[1] will retrieve 43 articles by Danks et al. on 28 different biochemical genetic problems (Appendix A); there are many more articles, editorials, reviews, chapters, conference proceedings, and letters on a wide spectrum of genetic topics—862 in all! Clinical phenotypes implicate genes involved in the pathogenesis of a trait, and they represent the classical mode of "forward genetics." Biochemical geneticists subscribe to a different approach, new when it was introduced half a century ago, that can actually lead to the gene by unravelling metabolic disturbance, from which a cellular function is identified, and so to the protein controlling that function; by decoding the primary sequence of the protein, or by isolation of the corresponding mRNA, one reaches the gene (functional cloning). Biochemical and somatic cell genetics are approaches that solve clinical problems, interpret the medical model of disease by linking manifestations to pathogenesis and cause, and offer opportunities for screening (in populations), testing (in families), diagnosis (in cases), and rational approaches to treatment and prevention. Danks et al. contributed to our understanding of: deoxyribose-5-phosphate aldolase deficiency (OMIM 125460); hawkinsinuria, a form of hypertyrosinemia (140350); trimethylaminuria (136131); prolidase deficiency (170100); osteogenesis imperfecta (OMIM 120160, 166200, 166220, 259400, and 259420); 3-hydroxy-3-methylglutaric aciduria (OMIM 246450); medium chain acyl dehydrogenase deficiency (201450), dihydrofolate reductase deficiency (126060); DOPA-responsive dystonia (128230); homocystinuria due to cystathionine β-synthase deficiency (OMIM 236200); succinic semialdehyde dehydrogenase deficiency (271980); methacrylic aciduria due to β-hydroxyisobutyryl CoA deacylase deficiency (250620); ornithine transcarbamylase deficiency (311250); nonketotic hyperglycinemia (238300); the "malignant" forms of hyperphenylalaninemia due to tetrahydrobiopterin dyshomeostasis (261630); Wilson disease (277900); Menkes disease (309400); pyruvate dehydrogenase deficiency (E_1 alpha subunit) (312170); fragile-X disorder (309550); and various "mitochondriopathies" (516003 and 540000). In the course of these studies, the Melbourne group pioneered gas chromatography-mass spectrometry as an investigative tool. Their seminal work on Menkes disease culminated in cloning the gene and characterizing its product.

II

Knowledge about hereditary metabolic disease expanded enormously during the three decades encompassed by Danks' career. After the rediscovery of Garrod's concepts [Beadle, 1959] and through the prosyletizing of human biochemical genetics by Harris [1959], there was an influx of converts to the field, along with the emergence of powerful new technolo-

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[1]OMIM is the continous online version of *Mendelian Inheritance in Man* [McKusick, 1994].

gies; a growth industry had been predicted [Penrose, 1959], and it occurred. The impact of molecular genetics on human genetic research and medicine in the 1980s and 1990s is the counterpart of biochemical genetics in the 1950s and 1960s.

The Metabolic Basis of Inherited Disease was first published in 1960 in response to the "astonishing growth of knowledge in human biochemical genetics" [Stanbury et al., 1960]. The seventh edition of "Stanbury" appeared in December 1994 [Scriver et al., 1995a]; David Danks, the author of its authoritative chapter on Menkes and Wilson diseases, is in the company of 301 other authors writing on 475 distinctive Mendelian "metabolic" disorders in 154 chapters spread over 4,605 pages of text in three volumes! The title of the seventh edition was changed to *The Metabolic and* Molecular *Bases of Inherited Disease.* Expansion of information and the changing focus in this book are fallouts from the discovery of the DNA double helix, the emergence of powerful recombinant DNA technologies, and the massive recruitment of converts to molecular biology and genetics. The progression from "inborn errors of metabolism" to "human biochemical genetics" to "metabolic and molecular bases of inherited disease" seems logical and inevitable; it also begs the question, "What are the limits of a 'metabolic' basis?"

III

McInnes and Byers [1993] said that genes cloned will soon outnumber genes understood by a huge margin; that familiar proteins may be given new life when their genes are localized to genetically defined loci; and that genes become candidates for components of genetic disease when mutations impair function of their products, or when disease and gene both map to the same locus. The message is clear: genome research, molecular cell biology, and biochemical genetics need one another.

Genomics is powerful, and the genome project is producing maps (genetic, chromosomal, and physical) that will eventually encompass all of OMIM and more. While the maps give guidance, complexity is everywhere. For example, the Melbourne biochemical geneticists were among the first to show that hyperphenylalaninemia per se, a single-variant metabolic phenotype, reflects locus heterogeneity involving either steps in tetrahydrobiopterin synthesis, its recycling, or phenylalanine hydroxylase integrity [Scriver et al., 1995b]. On the other hand, allelic variation at a single locus can confer widely diverse phenotypes, as illustrated by *RET* and several other genes [Romeo and McKusick, 1994]. Beyond the Garrodian pathways, cycles and networks of intermediary metabolism, biochemical geneticists now investigate signal transduction pathways encoded by oncogenes; cascades and networks of *trans*- and *cis*-acting transcription regulation of gene expression; and pathways of differentiation and development involving hierarchies, multifactor transcription control, positional information, and signal transduction. Each phenomenon, in its own way, involves a component of homeostasis, the central theme of evolution where genes propose and experiences dispose. Whereas molecular genetics is now the most powerful reductive tool that biologists can use, it is the homeostatic systems that need to be understood. Animal models, notably in mice [Paigen, 1995; Searle et al., 1994], whether natural, transgenic, or knockout, can test the salience of our genetic hypotheses. The ultimate goal is to know the "physiological genetics" involved [Scriver, 1987].

While modern biology is taking us inside objects which formerly could only be examined from the outside, we realize that an organism is the result of networks accommodating enormous complexities of molecular and energy fluxes. Living systems, with capacities for division, differentiation, movement, and communication, and with a finite lifespan (death *is* an essential feature of life), are objects functioning at far from equilibrium, separated from the world of chemical equilibrium by wondrous instabilities [Prigogine, 1980]. Organisms acquire a coherent state of matter, and they reproduce and renew complex molecules such as DNA and protein by integrated cellular processes. A living system is thermodynamically open, with a flow of energy passing through it and molecules in flux at every moment. The whole is a network of parts (dissipative structures) formed by a population of active macromolecules with a very high degree of communication between each other. *What happens* in these complex systems is the domain of molecular genetics, but when examined in their parts, this may only be a "virtual reality." *Why it happens* is more elusive, and progress in that direction is what I imagine will be the next revolution in biology. It will be about the reality of living systems. The corresponding revolution in human genetics will come when physiology reestablishes its roots in general biological theory to create a physiological or evolutionary genetics that unifies molecular biology and medicine. Training and education in medicine will have to move in the same direction if medical scientists are to retain their identity and credibility, and that will be a major challenge facing the Murdoch Institute in the era after Danks.

IV

Can one predict how research on inborn errors of dynamic cellular processes will evolve? Several themes come to mind, each reflecting an interest of the Melbourne group.

The Problem of Dominance

Dominant inheritance has been a recurrent and provocative theme in genetics. Variant alleles, unless neutral or adaptive, tend to be negatively selected. By what mechanism does a dominant allele affect phenotype, and why are dominant disorders so prevalent in OMIM? The questions are relevant not only to understand dominantly inherited *metabolic* traits (which are uncommon relative to the recessives), but also to understand the somatic cell genetics of cancer, for example.

The sensitivity coefficient. Kacser and Burns [1981] proposed that dominant metabolic disorders reveal the relative importance (sensitivity coefficient) of

the mutant enzyme for flux and homeostasis through the system (think of the LDL receptor in the endogenous cholesterol transport pathway). Thus, the occurrence of hyperprolinemia in heterozygotes with type 1 hyperprolinemia (proline oxidase deficiency), but not in those with type 2 hyperprolinemia (Δ' pyrroline-5-carboxylase deficiency), reflects the different types of fluxes involved [Phang et al., 1995]. The former is a one-enzyme pathway with a correspondingly high sensitivity coefficient for proline oxidase, whereas type 2 hyperprolinemia has a more complex network of fluxes and a lower sensitivity coefficient for the ΔP5C enzyme. The predicted gene dose effect on proline flux in the heterozygote, in the former case, is on the order of 50% impairment, but is much less in the second.

Trans-*acting effects.* Hawkinsuria, a strange disorder of tyrosine metabolism (OMIM 140350), is a dominant trait probably because of a *trans*-acting inhibitory effect on p-HPPA oxidase by an unusual metabolite. The theme of *trans*-acting (metabolite) effects in the phenotype of a hereditary metabolic disease has also emerged in type 1 hereditary tyrosinemia (OMIM 276700) and X-linked hypophosphatemia (OMIM 307800).

Dominant-negative mutation effect. Osteogenesis imperfecta (OI), a heterogeneous phenotype, was classified into dominant and recessive subtypes by the Melbourne group. Subsequent work at the molecular level indicated that most cases of OI, regardless of "type," are heterozygotes, and that phenotype is the result of a dominant effect. Some OI mutations cause the phenotype by a process analogous to the dominant-negative mutation effect on hetero- or homopolymers [Herskowitz, 1987]. The dominant-negative effect has also been invoked to explain excessive loss of enzyme activity in heterozygotes harboring mutations at either the phenylalanine hydroxylase, dihydropteridine reductase, or 6-pyruvoyltetrahydropterin synthase locus [Scriver et al., 1995b], all problems that were of interest to the Melbourne group.

Haplotype insufficiency or gain-of-function effects. Other molecular mechanisms of dominance that have attracted attention during the decades of Danks' career include haplotype insufficiency and gain-of-function. One or the other mechanism appears to underlie important dominantly inherited "metabolic" problems such as familial cancer and Huntington disease, and are likely to involve processes of signal transduction, or else transcription regulation of gene expression.

Mutation Detection

In an era when disease-producing genes are being cloned, the need for mutation detection is a natural sequel. The Melbourne paper on systematic approaches to mutation detection [Cotton, 1993] is a classic and was one of the first on this topic. Although the major efforts in mutation detection focus on genomic DNA, initiatives starting with mRNA are also of interest. "Illegitimate" transcription by reverse PCR of rare untranscribed mRNA species, e.g., in leukocytes, will allow mutation detection in the surrogate of the tissue primarily affected by the disease.

Tissue-Specific Phenomena

Analysis of abundant, tissue-specific mRNA species is one way to discover genes important in the function of that tissue. It is an alternative to functional, positional, and candidate-gene approaches to gene cloning [Collins, 1995]. Meanwhile, the study of tissue-specific disease will remain fruitful.

The eye is affected in about 30% of Mendelian traits [Costa et al., 1985], and the study of genetic eye disease demonstrates disease-producing allelic and locus heterogeneity in genes important for the development and function of the eye. To illustrate, *choroidoremia* was the first example of a metabolic interlock between sterol prenylation, GPTases of the Ras-protein superfamily, and retinal function. *Retinoblastoma* was the first solid tumor to be explained by loss of a cancer-suppressor gene and haplotype insufficiency. *Aniridia* was the first human malformation known to involve a homeobox-containing gene in a developmental program. *Leber's hereditary optic neuritis* was the first disease attributed to mutation in the mitochondrial genome. The molecular basis of *color vision* and *color blindness* was uncovered by molecular genetic methods; and *color sense,* a behavioral trait, can now be attributed to polymorphic variation in red and green photopigment genes. Recognition of locus heterogeneity in *retinitis pigmentosum* and *ectopia lentis* proved essential for diagnosis, counselling, and treatment. In brief, tissue-specific genetic diseases are microcosms of all forms of genetic disease, while demonstrating programs of development and function in the particular tissue.

V

There are five essential questions in medical practice: what is wrong (diagnosis); what is going to happen (prognosis); what can be done (treatment); why did it happen (prevention/cause)?[2] The fifth is the question I ask myself most often: why does this person have this disease now? As social and environmental conditions improve, the heritability of human disease will rise. That our major diseases have biological origins [Sorensen et al., 1988] and that genetic disease is prevalent [Baird et al., 1988] are no longer matters for dispute, as they were when Garrod [1931] proposed inherited susceptibility to disease. Accordingly, there is every reason to want to understand how homeostasis is perturbed by the disease process, how it can be restored by treatment, and best of all, how to prevent any disturbance at all by addressing its causes. Hereditary metabolic disease is a subset of human disease about which more is known than almost any other disease. Therefore, one would expect that treatment of heredi-

[2]Victor McKusick introduced me to these four questions; the fifth has been the subject of 20 years' discussion with Barton Childs.

tary metabolic disease would be highly effective. Unfortunately it is not uniformly so [Treacy et al., 1995] because we do not know well enough how to restore homeostasis when it is undermined by biological variation. Accordingly, research on animal models of human disease [Paigen, 1995; Searle et al., 1994], somatic-cell gene therapy, the design of drugs (orphan and otherwise), and molecular therapy to modify gene expression will see an influx of converts and another growth industry in allied technologies.

Science is an assault on ignorance, yet what science knows is less interesting than what it does not yet know, and that is certainly true in genetics [Ridley, 1991; Scriver, 1993]. Society tolerates geneticists on the understanding that they will eventually convert enigmas about life into facts, and the facts into useful applications to benefit individuals and society. And there lies the problem: what applications, and how will they be used?

Society has concerns about genetics in two broad areas. First, do geneticists play God or behave like Nazis (two metaphors oddly interchangeable)? Second, do geneticists tamper with the integrity of nature? It ought now to be apparent that if geneticists are gods, they are rather impotent by comparison with the classical examples. And if they are tampering with nature's integrity, they are awfully late into the game and have a lot to learn from Nature, the magnificent tinkerer.

In the Murdoch Institute, the physician and the scientist can work side by side, if not actually inhabiting the same body. However, there are significant differences in our expectations of a scientist and a physician:

The scientist attacks ignorance and pushes at the limits of knowledge. The physician must know what is known and use it.

Science is a collegial and public activity—usually; medical practice is a private relationship between physician and patient—always.

Scientists are driven by hypotheses; physicians must make decisions and act on whatever facts are available, no matter how limited they are.

David Danks may be one of the last of an endangered species, the physician-scientist. At the Murdoch Institute there has been an effective marriage between science and medicine, a marriage that somehow has to endure as the science gets tougher and medicine more complex. While congratulations are in order for what is past, what can be said about the future at a celebration like this? My hope is that scientists and physicians will increasingly share a common language, the language of biology in medicine. Barriers between science and medicine will then be lowered and the patient will benefit, provided medicine does not lose its way and molecular medicine allows us to get back to that ever-challenging organism, the patient. Perhaps the new Director will distribute Immanual Kant's two famous aphorisms for all to see: What can I know (an enduring question, even for molecular geneticists)? What ought I do (a question faced by the physician-scientist with every patient)? These are the major questions David Danks hands on to his successor at the Murdoch Institute. Well done and good luck.

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McKusick VA (1994): "Mendelian Inheritance in Man: A Catalog of Human Genes and Genetic Disorders," 11th ed. Baltimore: Johns Hopkins University Press, pp.

Paigen K (1995): A miracle enough: The power of mice. Nat Med 1:215–220.

Penrose LS (1959): Preface. In Harris H: "Human Biochemical Genetics." Cambridge, UK: Cambridge, University Press.

Phang JM, Yeh GC, Scriver CR (1995): Disorders of proline and hydroxyproline metabolism. In Scriver CR, Beaudet AL, Sly WS, Valle D (eds): "The Metabolic and Molecular Bases of Inherited Disease." New York: McGraw-Hill Book Co., pp 1125–1146.

Prigogine I (1980): "From Being to Becoming. Time and Complexity in the Physical Sciences." New York: WH Freeman and Co.

Ridley M (1991): The edge of ignorance. Economist Feb 16; A survey of science. 1–22.

Romeo G, McKusick VA (1994): Phenotype diversity, allelic series and modifier genes. Nat Genet 7:451–453.

Scriver CR (1987): Presidential address: Physiological genetics—Who needs it? Am J Hum Genet 40:199–211.

Scriver CR (1993): Genetics and society: What society expects of geneticists—Overview. Trans R Soc Can 4:121–127.

Scriver CR, Beaudet AL, Sly WS, Valle D (eds) (1995a): "The Metabolic and Molecular Bases of Inherited Disease. 7th ed." New York: McGraw-Hill Book Co., pp i–xxxvi;1–4605.

Scriver CR, Kaufman S, Eisensmith RC, Woo SLC (1995b): The hyperphenylalaninemias. In Scriver CR, Beaudet AL, Sly WS, Valle D (eds): "The Metabolic and Molecular Bases of Inherited Disease. 7th ed." New York: McGraw-Hill Book Co., pp 1015–1075.

Searle AG, Edwards JH, Hall JG (1994): Mouse homologues of human hereditary disease. J Med Genet 31:1–19.

Sorensen TIA, Nielsen GG, Andersen PK, Teasdale TW (1988): Genetic and environmental influences on premature death in adult adoptees. N Engl J Med 318:727–732.

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metabolic disease: 1993 survey and 10-year comparison. Am J Hum Genet 56:359–367.

APPENDIX A

Publications on Biochemical Genetics Topics by David Danks et al. in the Melbourne Group, Listed by OMIM Number

120160 Collagen, type I, alpha-2 chain (COL1A2; collagen of skin, tendon, and bone, alpha-2 chain)

Sillence DO, Senn A, Danks DM (1979): Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 16:101–116.

125460 deoxyribose-5-phosphate aldolase deficiency

Chappel A, Scholem RD, Brown GK, Truscott RM, Cotton RGH, Haan EA, Danks DM (1983): Deoxyribose-5-phosphate aldolase deficiency—A harmless inborn error of metabolism. J Inherited Metab Dis 6:105–107.

Truscott RJW, Halpern B, Hammond J, Hunt SM, Cotton RGH, Haan EA, Danks DM (1979): A defect in deoxyribose metabolism. N Engl J Med 300:1115.

Truscott RJW, Halpern B, Hammond J, Hunt SM, Cotton RGH, Haan EA, Danks DM (1979): Abnormal deoxyribose metabolites in the urine of a child with a possible new inborn error of metabolism. Biomed Mass Spectrom 6:453–459.

126060 dihydrofolate reductase (DHFR; Megaloblastic anemia due to dihydrofolate reductase deficiency, included; DHFR deficiency, included)

Tauro GP, Danks DM, Rowe PB, Van der Weyden MB, Schwarz MA, Collins VL, Neal BW (1976): Dihydrofolate reductase deficiency causing megaloblastic anemia in two families. N Engl J Med 294:466–470.

128230 dystonia, progressive, with diurnal variation (Segawa syndrome; dystonia-parkinsonism with diurnal fluctuation; dystonia, DOPA-responsive; DOPA-responsive dystonia; DRD)

Danks DM (1986): Melbourne, Australia: Personal communication.

136131 flavin-containing monooxygenase 2 (FMO2; FMO, adult liver form; trimethylamine oxygenase; TMA oxygenase; trimethylaminuria, included; fish-odor syndrome, included)

Danks DM, Hammond J, Faull K, Burke D, Halpern B (1976): Trimethylaminuria: Diet does not always control the fishy odor. N Engl J Med 295:962.

140350 hawkinsinuria (4-@hydroxyphenylpyruvate hydroxylase deficiency)

Danks DM, Tippett P, Rogers J (1975): A new form of prolonged transient tyrosinemia presenting with severe metabolic acidosis. Acta Paediatr Scand 64:209–214.

Niederwieser A, Matasovic A, Tippett P, Danks DM (1977): A new sulfur amino acid, named hawkinsin, identified in a baby with transient tyrosinemia and her mother. Clin Chim Acta 76:345–356.

166200 osteogenesis imperfecta with blue sclerae (OI type I; osteogenesis imperfecta tarda)

Sillence DO, Senn A, Danks DM (1979): Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 16:101–116.

166220 osteogenesis imperfecta with normal sclerae (OI type IV)

Sillence DO, Senn A, Danks DM (1979): Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 16:101–116.

170100 peptidase D (PEPD; prolidase; imidodipeptidase; prolidase deficiency, included)

Endo F, Tanoue A, Kitano A, Arata J, Danks DM, Lapiere CM, Sei Y, Wadman SK, Matsuda I (1990): Biochemical basis of prolidase deficiency: Polypeptide acid RNA phenotypes and the relation to clinical phenotypes. J Clin Invest 85:162–169.

Sheffield LJ, Schlesinger P, Faull K, Halpern BJ, Schier GM, Cotton RGH, Hammond J, Danks DM (1977): Iminopeptiduria, recurrent skin ulcerations and edema in a boy with prolidase deficiency. J Pediatr 91:578–583.

201450 acyl-CoA dehydrogenase, medium-chain, deficiency of (ACADM deficiency; MCAD deficiency; hypoglycemia, nonketotic, and carnitine deficiency due to medium-chain acyl-CoA dehydrogenase deficiency; carnitine deficiency secondary to medium-chain acyl-CoA dehydrogenase deficiency; MCADH deficiency, dicarboxylicaciduria due to; dicarboxylicaciduria due to defect in beta-oxidation of fatty acids)

Matsubara Y, Narisawa K, Miyabayashi S, Tada K, Coates PM, Bachmann C, Elsas LJ II, Pollitt RJ, Rhead WJ, Roe CR (1990): Identification of a common mutation in patients with medium-chain acyl-CoA dehydrogenase deficiency. Biochem Biophys Res Commun 171:498–505.

214100 cerebrohepatorenal syndrome (CHR syndrome; Zellweger syndrome; ZS; ZWS; ZWS1)

Danks DM, Tippett P, Adams C, Campbell P (1975): Cerebro-hepato-renal syndrome of Zellweger: A report of eight cases with comments upon the incidence, the liver lesion, and a fault in pipecolic acid metabolism. J Pediatr 86:382–387.

236200 homocystinuria (cystathionine-beta-synthase deficiency; CBS deficiency; CBS, included; pyridoxine-responsive mocystinuria, included)

Shipman RT, Townley RRW, Danks DM (1969): Homocystinuria, Addisonian pernicious anaemia, and partial deletion of a G chromosome. Lancet II:693–694.

238300 hyperglycinemia, isolated nonketotic, type I (NKH1; glycine cleavage system, P protein, included; GCS, P protein, included; GCSP, included; glycine decarboxylase, included; glycine dehydrogenase, included; GLDC, included)

Nanao K, Okamura-Ikeda K, Motokawa Y, Danks DM, Baumgartner ER, Takada G, Hayasaka K (1994): Identification of the mutations in the T-protein gene causing typical and atypical nonketotic hyperglycinemia. Hum Genet 93:655–658.

246450 leucine metabolism, defect in (3-@hydroxy-3-methylglutaryl CoA lyase deficiency; HMG-CoA lyase deficiency; HL deficiency; hydroxymethylglutaricaciduria; HMGCL, included)

Faull K, Bolton P, Halpern B, Hammond J, Danks DM, Hahnel R, Wilkinson SP, Wysocki SJ, Masters PL (1976): Patient with defect in leucine metabolism. N Engl J Med 294:1013.

Faull KF, Bolton PD, Halpern B, Hammond J, Danks DM (1976): The urinary organic acid profile associated with 3-hydroxy-3-methylglutaric aciduria. Clin Chim Acta 73:553–559.

248360 malonyl CoA decarboxylase deficiency

Brown GK, Scholem RD, Bankier A, Danks DM (1984): Malonyl coenzyme A decarboxylase deficiency. J Inherited Metab Dis 7:21–26.

250620 methacrylicaciduria (methacrylic acid toxicity; beta-hydroxyisobutyryl CoA deacylase, deficiency of; valine metabolic defect)

Brown GK, Hunt SM, Scholem R, Fowler K, Grimes A, Mercer JFB, Truscott RM, Cotton RGH, Rogers JG, Danks DM (1982): Beta-hydroxyisobutyryl coenzyme A deacylase deficiency: A defect in valine metabolism associated with physical malformations. Pediatrics 70: 532–538.

259400 osteogenesis imperfecta congenita (OIC; Vrolik type of osteogenesis imperfecta; OI type II, recessive form; lethal perinatal OI)

Sillence DO, Senn A, Danks DM (1979): Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 16:101–116.

259420 osteogenesis imperfecta, progressively deforming, with normal sclerae (OI type III)

Sillence DO, Senn A, Danks DM (1979): Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 16:101–116.

261630 phenylketonuria II (dihydropteridine reductase deficiency; DHPR deficiency; PKU, atypical; quinoid dihydropteridine reductase deficiency; QDPR deficiency)

Dahl H-HM, Wake S, Cotton RGH, Danks DM (1988): The use of restriction fragment length polymorphisms in prenatal diagnosis of dihydropteridine reductase deficiency. J Med Genet 25:25–28.

Danks DM, Bartholome K, Clayton BE, Curtius H, Grobe H, Lemming R, Pfleiderer W, Rembold H, Rey F (1978): Malignant hyperphenylalaninaemia—Current status (June 1977). J Inherited Metab Dis 1:49–53.

Danks DM, Cotton RGH, Schlesinger P (1975): Tetrahydrobiopterin treatment of variant form of phenylketonuria. Lancet II:1043.

Danks DM, Schlesinger P, Firgaira F, Cotton RGH, Watson BM, Rembold H, Hennings G (1979): Malignant hyperphenylalaninemia—clinical features, biochemical findings, and experience with administration of biopterins. Pediatr Res 13:1150–1155.

Firgaira FA, Cotton RGH, Danks DM (1979): Dihydropteridine reductase deficiency: Diagnosis by assays on peripheral blood-cells. Lancet II: 1260–1263.

271980 succinic semialdehyde dehydrogenase deficiency (SSADH deficiency; 4-@hydroxybutyricaciduria; GABA metabolic defect; gamma-hydroxybutyricaciduria)

Haan EA, Brown GK, Mitchell D, Danks DM (1986): Succinic semialdehyde dehydrogenase deficiency—A further case. J Inherited Metab Dis 8:99.

277900 Wilson disease (WND; WD; hepatolenticular degeneration; ATPase, Cu(2+)-transporting, beta polypeptide, included; ATP7B, included)

Danks DM, Metz G, Sewell R, Prewett EJ (1990): Wilson's disease in adults with cirrhosis but no neurological abnormalities. Br Med J [Clin Res] 301:331–332.

309400 Menkes syndrome (kinky hair disease; steely hair disease; copper transport disease; MK; MNK)

Camakaris J, Danks DM, Ackland L, Cartwright E, Borger P, Cotton RGH (1980): Altered copper metabolism in cultured cells from human Menkes' syndrome and mottled mouse mutants. Biochem Genet 18:117–131.

Danks DM (1988): The mild form of Menkes disease: Progress report on the original case. Am J Med Genet 30:859–864.

Danks DM, Campbell PE, Stevens BJ, Mayne V, Cartwright E (1972): Menkes' kinky hair syndrome: An inherited defect in copper absorption with widespread effects. Pediatrics 50:188–201.

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Danks DM, Stevens BJ, Campbell DE, Gillespie JM, Walker-Smith J, Bloomfield J, Turner B (1972): Menkes' kinky-hair syndrome. Lancet I:1100–1102.

Procopis P, Camakaris J, Danks DM (1981): A mild form of Menkes steely hair syndrome. J Pediatr 98:97–99.

Royce PM, Camakaris J, Danks DM (1980): Reduced lysyl oxidase activity in skin fibroblasts from patients with Menkes' syndrome. Biochem J 192:579–586.

311250 ornithine transcarbamylase deficiency, hyperammonemia due to (OTC; ornithine carbamoyltransferase deficiency; OCT deficiency; OCTD; valproate sensitivity, included)

Hoogenraad N, de Martinis M, Danks DM (1983): Immunological evidence for an ornithine transcarbamylase lesion resulting in the formation of enzyme with smaller protein subunits. J Inherited Metab Dis 6:149–152.

312170 pyruvate dehydrogenase complex, E1-alpha polypeptide-1 (PDHCE1A; PHE1A; PDHA; PDHA1; pyruvate dehydrogenase deficiency, included; ataxia, intermittent, with abnormal pyruvate metabolism, included)

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